physiology team 429

NEUROTRANSMITTERS

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NEUROTRANSMITTERS

DEFINITION:

1- Are chemical transducers which are released by electrical impulses into the synaptic cleft from presynaptic membrane vesicles.

2- It then diffuses to the postsynaptic membrane and reacts and activates the receptors present leading to initiation of new electrical signals.

Neurotransmitter Criteria

Neuroscientists have set up a few guidelines or criteria to prove that a chemical is really a neurotransmitter. Not all of the neurotransmitters that you have heard about may actually meet every one of these criteria.

The chemical must be produced within a neuron. 	The chemical must be found within a neuron. 	When a neuron is stimulated (depolarized), a neuron must release the chemical. 
When a chemical is released, it must act on a post-synaptic receptor and cause a biological effect. 	After a chemical is released, it must be inactivated. Inactivation can be through a reuptake mechanism or by an enzyme that stops the action of the chemical. 	If the chemical is applied on the post-synaptic membrane, it should have the same effect as when it is released by a neuron. 

Classification of Neurotransmitters

- ✓ Amines :

A. Acetyl choline (Ach)

B. Monoamines

- ✓ Catecholamines

– Epinephrine

– Nor epinephrine

– Dopamine (Substantia nigra , sympathetic ganglia)

- ✓ Serotonin (hypothalamus, cerebellum, spinal cord, retina)
- ✓ Histamine (Hypothalamus)

- ✓ Amino acids:

I. Excitatory :

Glutamate (cortex, brainstem)

Aspartate (visual cortex)

II. Inhibitory :

Gamma amino butaric acid GABA

(cerebrum, cerebellum [presynaptic inhibitory neurone in retina])

Glycine (spinal cord)

III. Purine derivatives

Adinosine & ATP.

IV. Polypeptides (a very long list of names)

Enkephaline

hormones (VIP etc)

(refer to the list in Ganong 21st edition pg.97)

V. Nonsynaptic transmitters

Gases

nitric oxide

cabon mono oxide.

Classification of Neurotransmitters

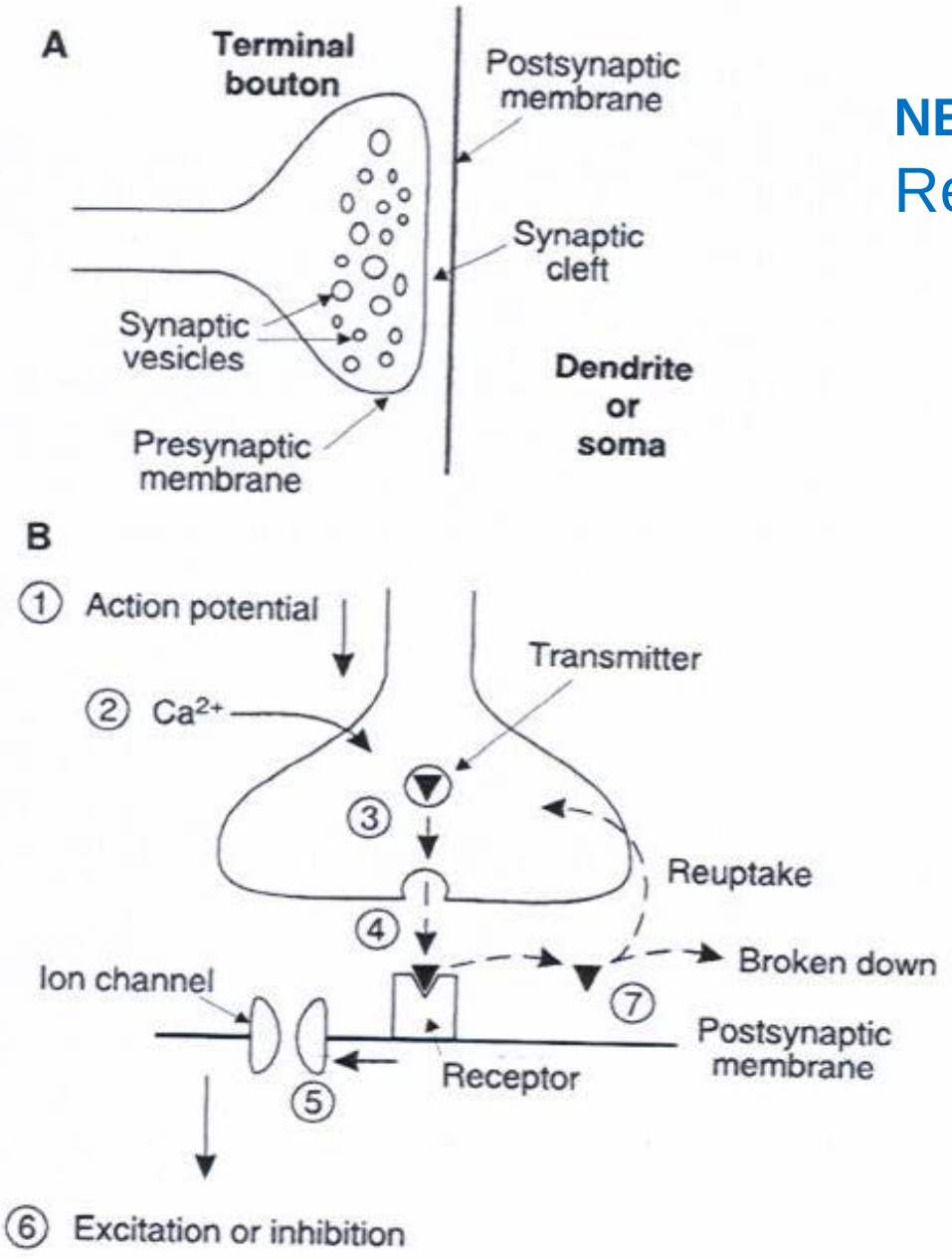
Amines		
Acetylcholine (ACh)	Dopamine (DA)	Norepinephrine (NE)
Serotonin (5-HT)	Histamine	Epinephrine

Amino Acids		
Gamma-aminobutyric acid (GABA)	Glycine	Glutamate
Aspartate		

Neuroactive Peptides - partial list!!			
bradykinin	beta-endorphin	bombesin	calcitonin
cholecystokinin	enkephalin	dynorphin	insulin
gastrin	substance P	neurotensin	glucagon
secretin	somatostatin	motilin	vasopressin
oxytocin	prolactin	thyrotropin	angiotensin II
sleep peptides	galanin	neuropeptide Y	thyrotropin-releasing hormone
gonadotropnin-releasing hormone	growth hormone-releasing hormone	luteinizing hormone	vasoactive intestinal peptide

Soluble Gases	
Nitric Oxide (NO)	Carbon Monoxide

NEUROTRANSMITTER :
Release and Action



- The Major steps in neurotransmitter processing are :

1- synthesis

2- storage

3- release

4- reception

5- inactivation

Fate of neurotransmitters

1. Consumed (broken down or used up)

At postsynaptic membrane leading to action potential generation.

1. Degraded

by enzymes present in synaptic cleft.

1. Reuptake

Mechanism(reutilization) this is the most common fate.

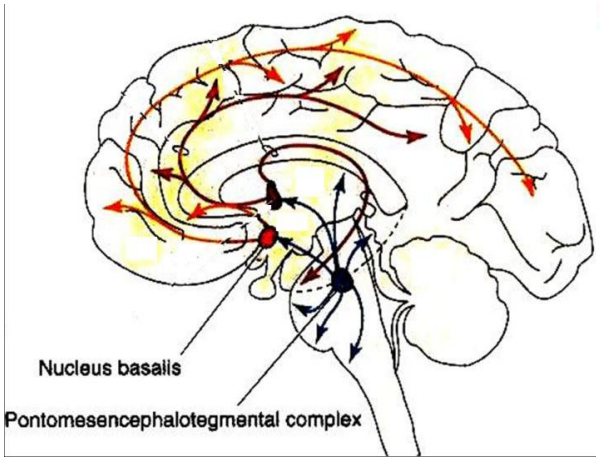
▪ Acetylcholine

A- Where is ACh found?

In the brain in →

(1) the Basal Forebrain

(mainly Nucleus Basalis)



•(2) Ponto-Mesencephalic Cholinergic Complex

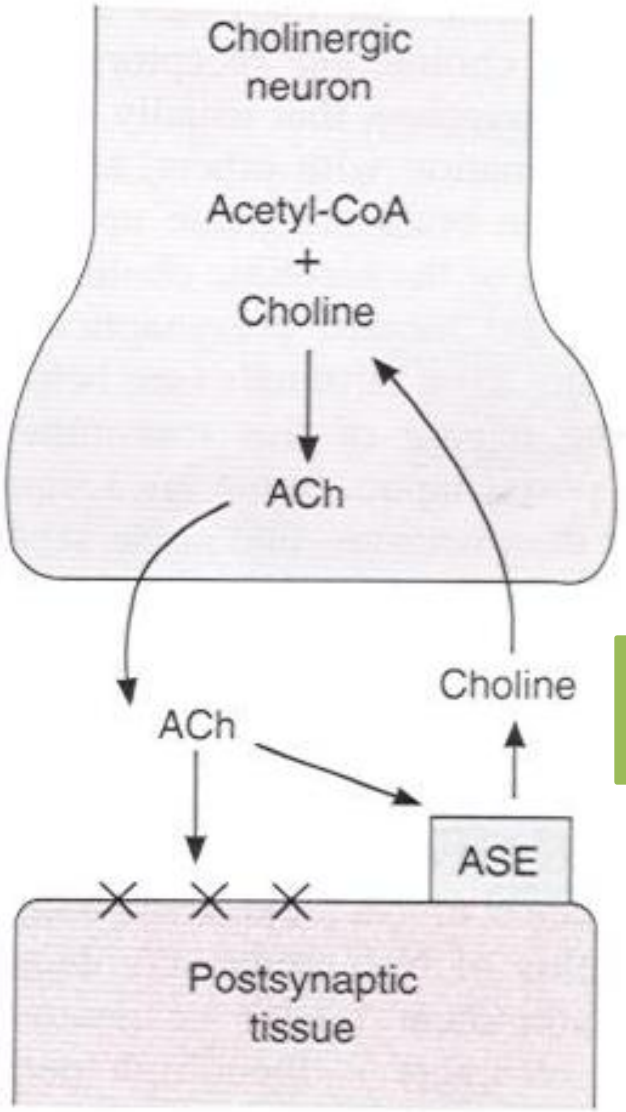
B- Functions of Acetylcholine

1-Cognitive functions such as: learning, memory, consciousness, arousal and attention.

It plays a role in the enhancement of sensory perception when we wake up.

[Damage of cholinergic system is associated with memory deficits associated with Alzheimer's disease]

2-Outside the brain, Ach is the main neurotransmitter in the parasympathetic system.



ASE = Acetylcholinesterase

C- Processing of Acetylcholine

- Synthesis of Ach involves the reaction between Choline & Acetyl-CoA (active acetate).

This reaction requires the enzyme *Cholineacetyltransferase*

- After being released into the synaptic cleft ACh opens **Na** channels to depolarize the postsynaptic membrane and then is rapidly hydrolyzed into Choline and Acetate by the action of the enzyme *Actylcholinesterase*.

Acetyl Choline Receptors

		Nicotinic	Muscarinic
1	Located at:	i. Neuromuscular junction of skeletal muscle ii. Postganglionic neurons of parasympathetic nervous system. iii. Ventral tegmental area.	i. Glands ii. Neuromuscular junctions of cardiac and smooth muscle. iii. Postganglionic neurons of sympathetic nervous system.
2	Agonist	Nicotine	Muscarine (a toxin produced by certain mushroom)
3	Antagonist	Curare (paralyses skeletal muscle)	Atropine

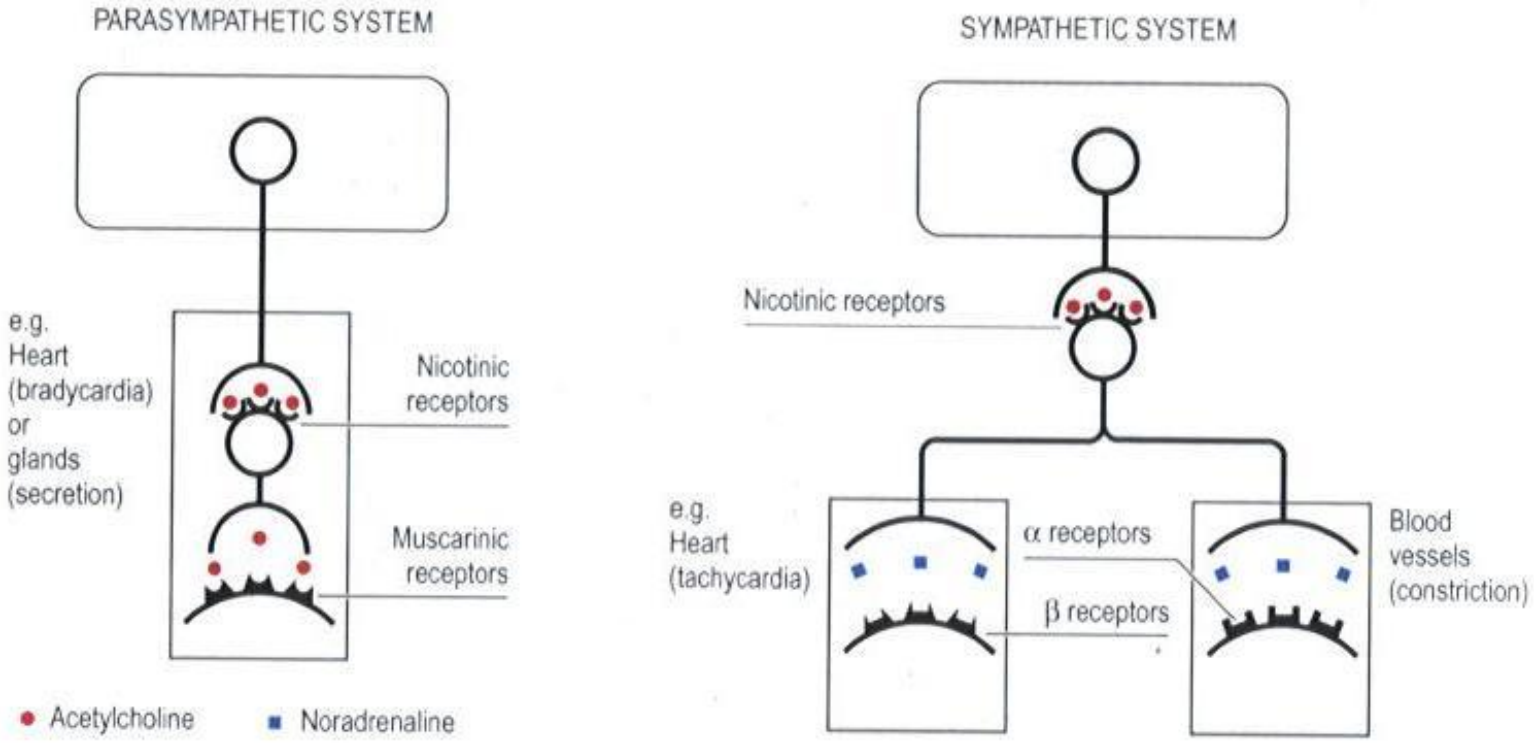


Fig. 3.2.8 The sites of release of the classical autonomic transmitters, acetylcholine and noradrenaline, and their receptors.

- **Monoamines Catecholamines**

(Epinephrine, Norepinephrine, Dopamine)

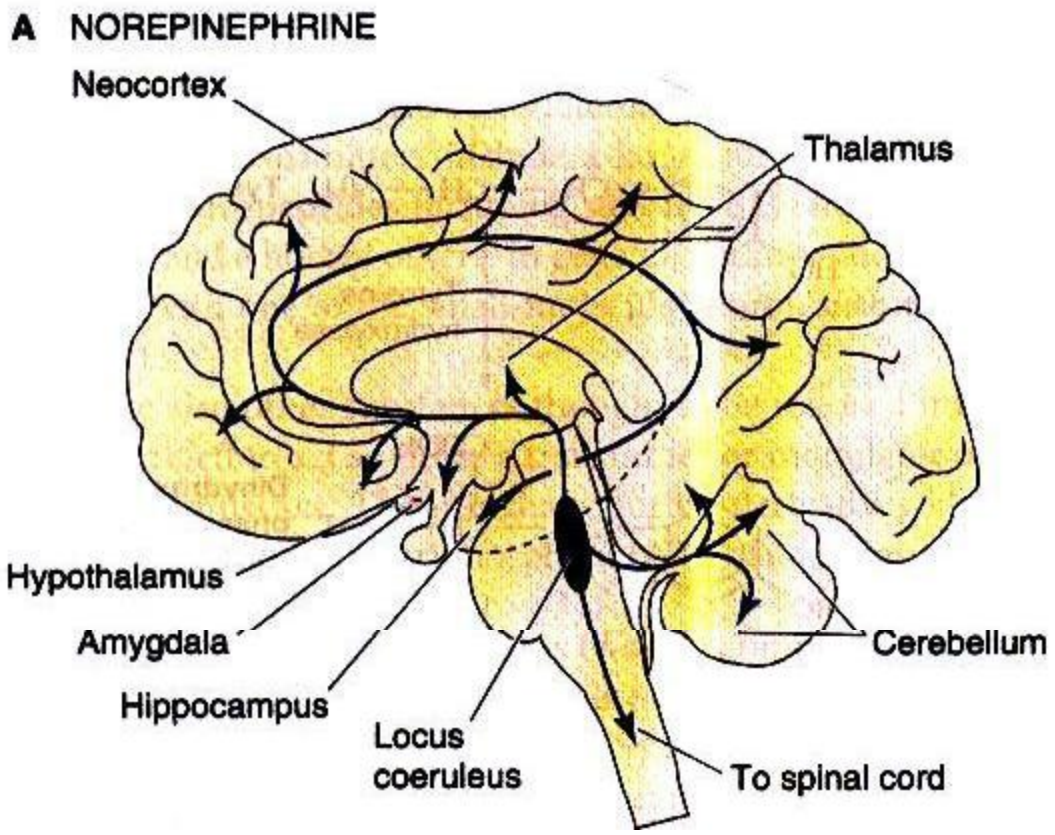
Epinephrine and Norepinephrine

A- Where are Epinephrine and Norepinephrine found?

The cell-bodies of Noradrenergic neurons are located mainly in the *Locus Coeruleus.*

- From the *Locus Coeruleus* the axons of noradrenergic neurons arborize widely, constituting the Locus Coeruleus System.

Epinephrine and Norepinephrine



B- Functions of NE and Epinephrine

1. Constitutes part of the **RAS**(Reticular Activating System) which regulates alertness
2. Plays a role in **fight or flight** situations, including competitive athletic behavior and aggressive behavior.
3. Blood pressure regulation.

[Norepinephrine and Serotonin deficiencies are implicated in the pathogenesis of **depression**]

The actions of noradrenaline are mainly inhibitory (β adrenoceptors), but some are excitatory (α- or β-adrenoceptors).

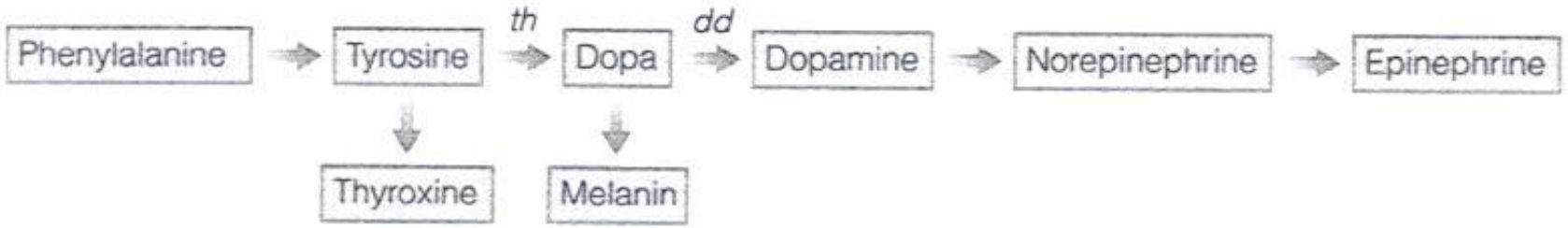
C- Processing of Catecholamines

- The three catecholamines are formed by hydroxylation and decarboxylation of the amino acid **Tyrosine**.

- *Tyrosine Hydroxylase* is the rate-limiting enzyme, and it is subject to feed-back inhibition by dopamine and norepinephrine, thus providing internal control of the synthesis process.

- Some neurons in the brain, and adrenal medullary cells contain in their cytoplasm the enzyme **PNMT** (*Phenylethanolamine N-methyltransferase*) which converts NE into epinephrine.

Epinephrine & Norepinephrine



Key Enzymes
th = tyrosine hydroxylase, rate limiting step
dd = dopa decarboxylase

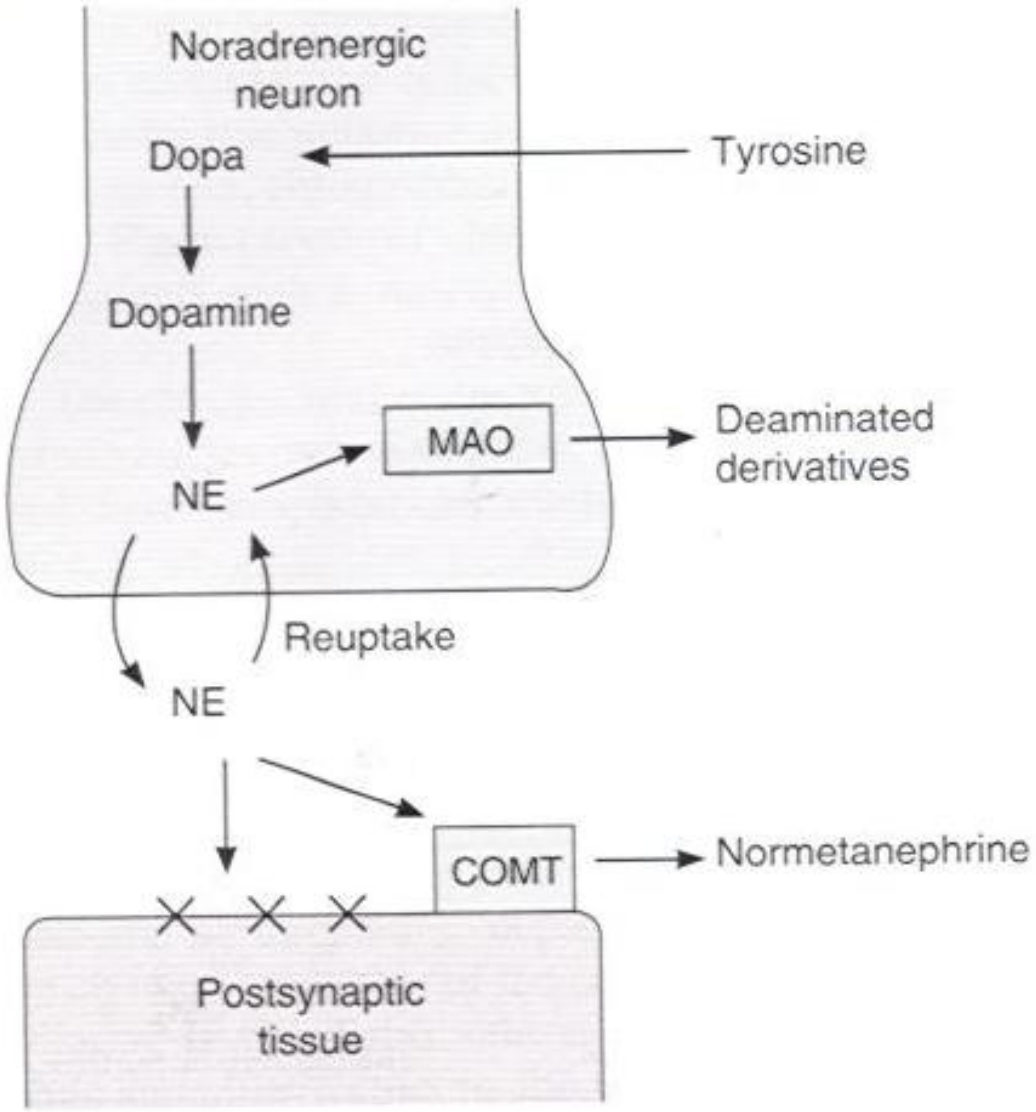
C- processing cont.

- NE is removed from the synaptic cleft by:

1) binding to postsynaptic receptors

2) reuptake into presynaptic neurons, where degraded intracellularly by the enzyme *Monoamine Oxidase* (**MAO**). >> the major mechanism of inactivation of NE

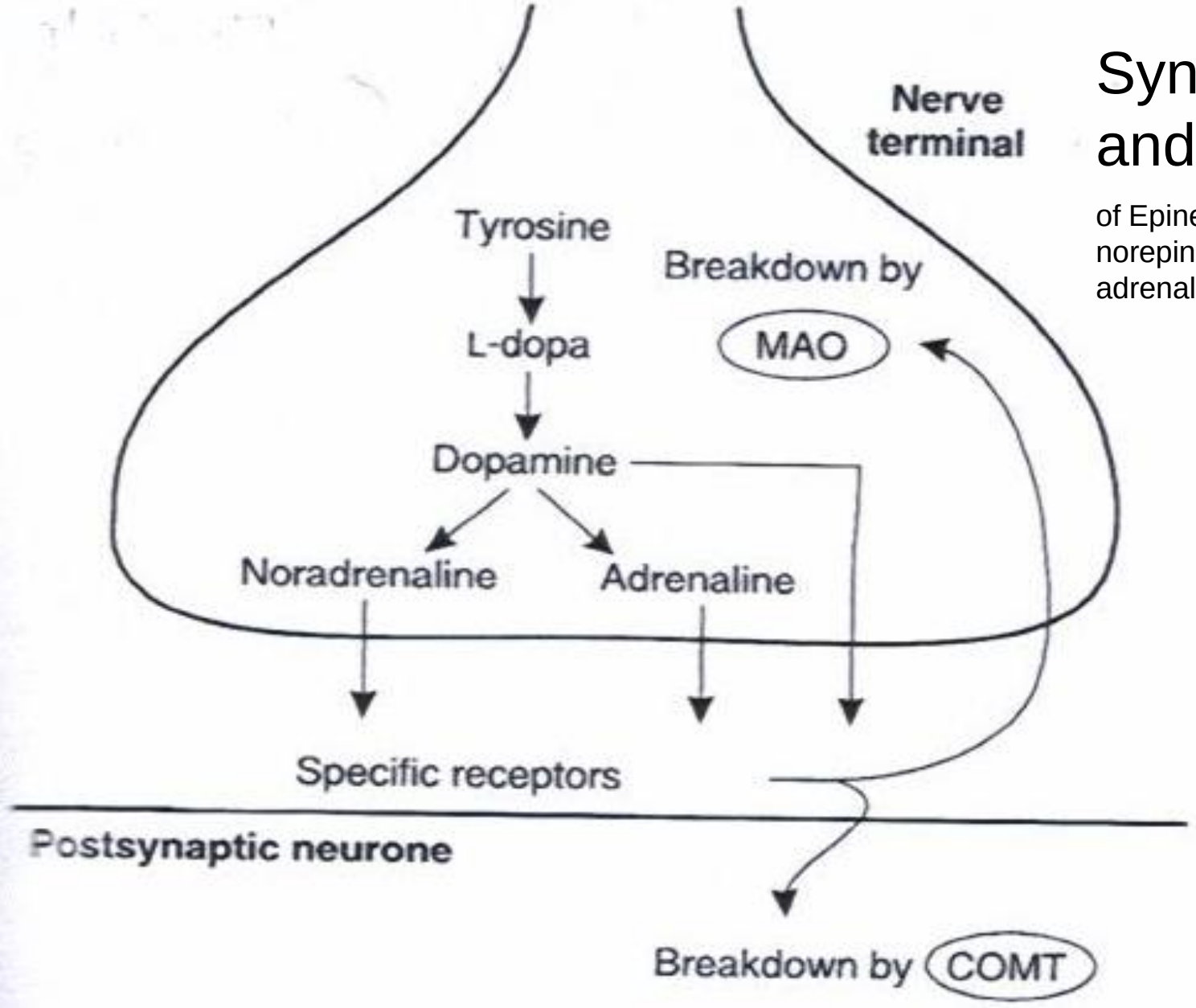
3) Inactivation by the enzyme *Catechol-O-Methyl-Transferase* (**COMT**) which is present on postsynaptic membrane (NOT presynaptic) and in larger amounts in glial cells.



Norepinephrine synthesis and fate at synapses

Synthesis and Fate

of Epinephrine and norepinephrine in adrenal medulla



MAO=monoamine oxidase ,COMT=catechole-o-methyle-transferase

▪Dopamine (DA)

-Monoamine neurotransmitter, concentrated in very specific groups of neurons called **basal ganglia**.

-acts on the chemoreceptor trigger zone to cause nausea and vomiting.

-Hormone release from the anterior pituitary gland is regulated by dopamine, especially *prolactin* release (inhibited) and *growth hormone* release (stimulated).

[Dopamine deficiency in the Basal Ganglia can lead to Parkinsonism]

-After being secreted into the synaptic cleft , reuptake takes place via a Na+ and Cl- dependent dopamine transporter .

- Dopamine is metabolized by MAO and COMT.

Dopaminergic Pathways

Dopaminergic pathways:

(A) **Nigrostriatal** System :

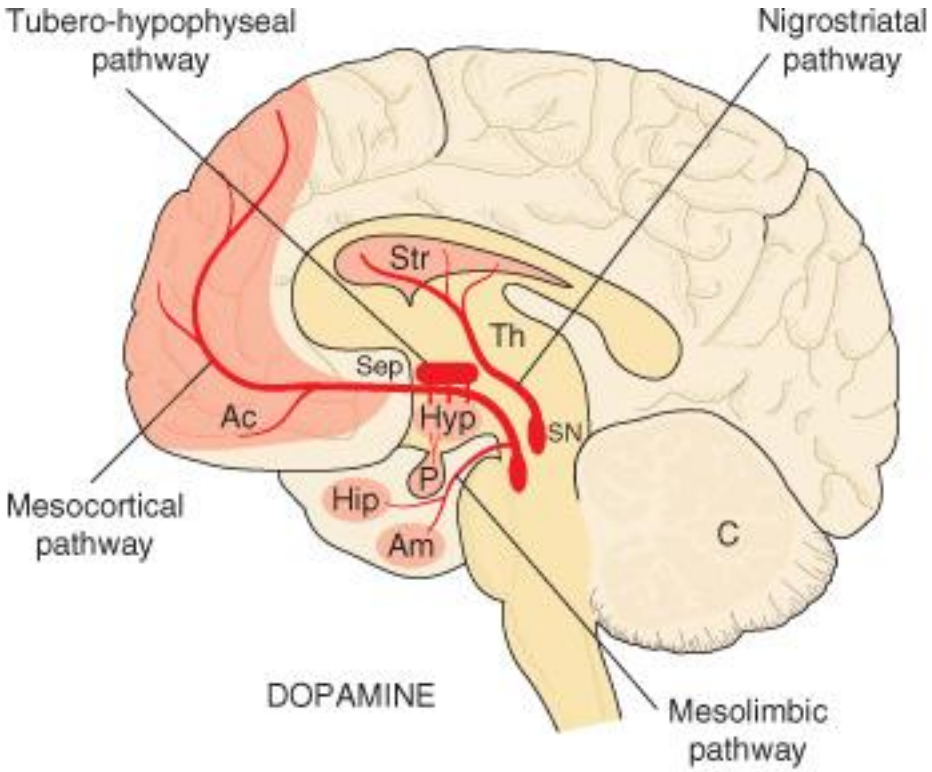
- Dopaminergic fibers originate in Substantia Nigra and project to the *Striatum*.
- This system is involved in motor control

(B) **Mesocortical / Mesolimbic** System :

- Dopaminegic fibers arises from the Ventral Tegmental Area

in the midbrain and projects to Nucleus Accumbens and Limbic System.

The Mesocortical System is involved in behaviors of emotion, drug-induced reward systems and Addiction.

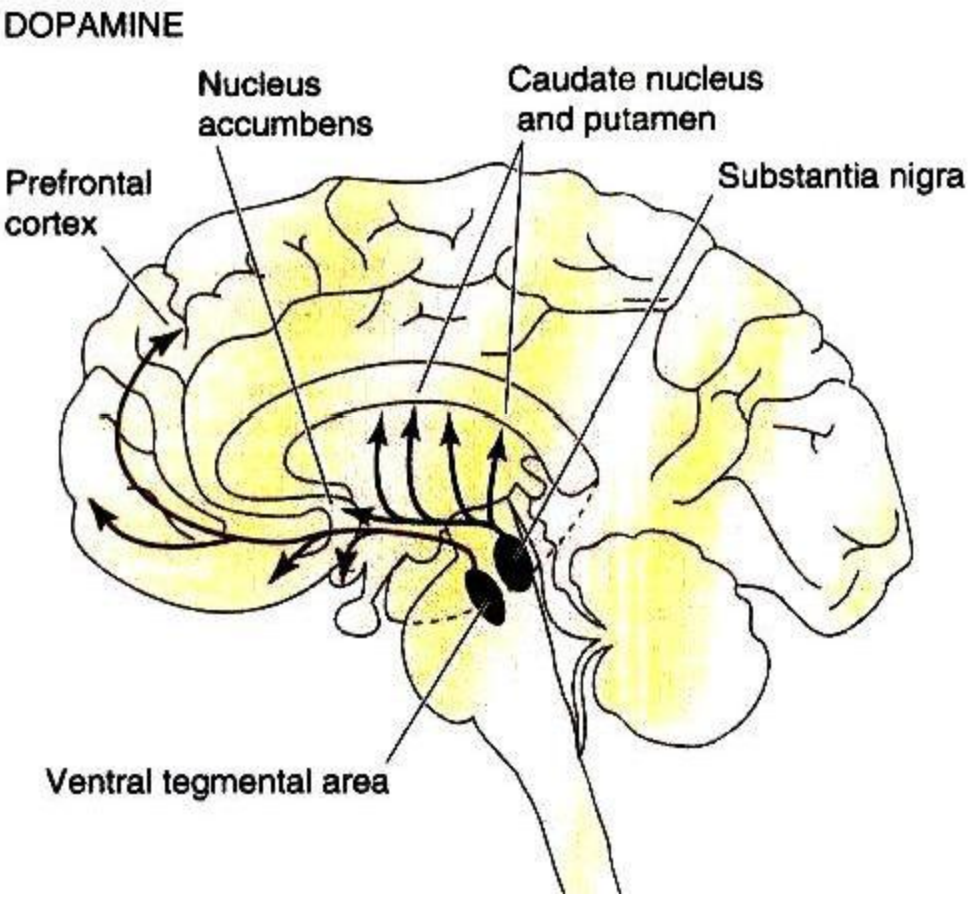


Dopaminergic Pathways

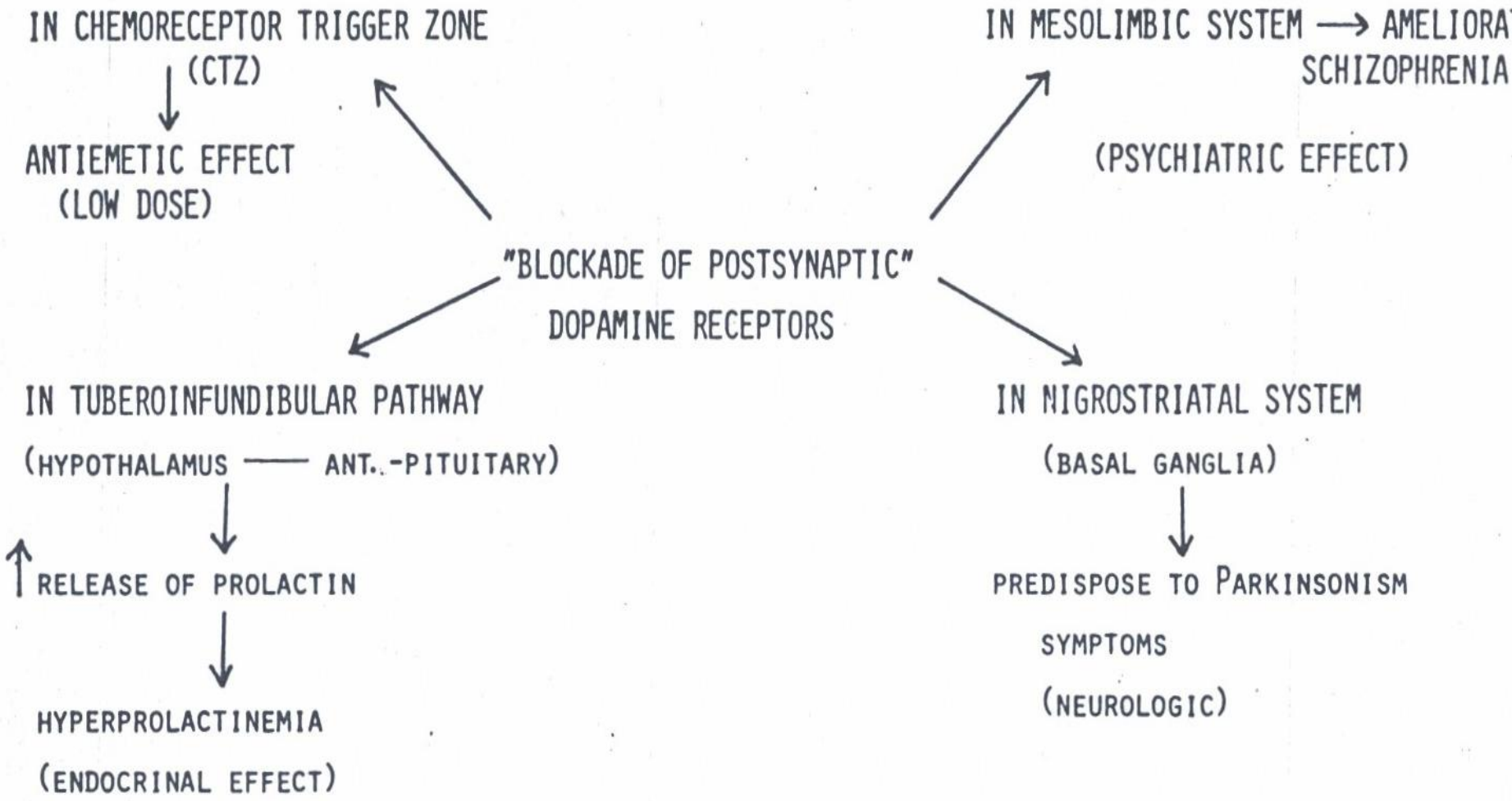
[Defect or overstimulation in the Mesocortical System could be responsible for the psychotic symptoms of Schizophrenia]

(C) **Tuberohypophyseal** neurons :

Running from the hypothalamus to the pituitary gland, the secretions of which they regulate


DOPAMINE
Nucleus accumbens
Caudate nucleus and putamen
Prefrontal cortex
Substantia nigra
Ventral tegmental area

EFFECTS ON DOPAMINERGIC SYNAPSES



THE SAME PHARMACODYNAMIC ACTION MAY HAVE DISTINCT PSYCHIATRIC "NEUROLOGIC" AND ENDOCRINE EFFECTS.

▪Serotonin

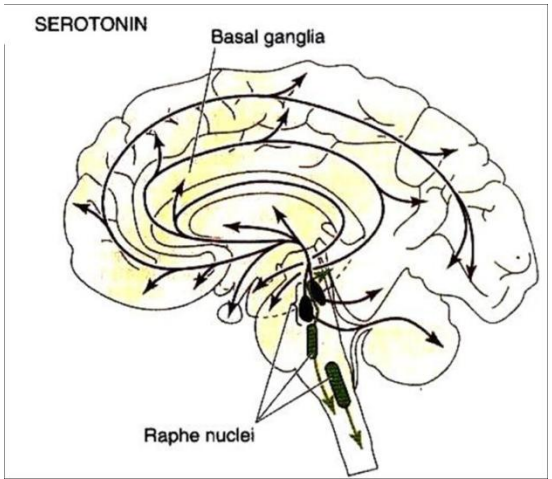
[Serotonin = 5-HT = 5 Hydroxytreptamine]

Brain Serotonin is present in the **Raphe Nuclei**

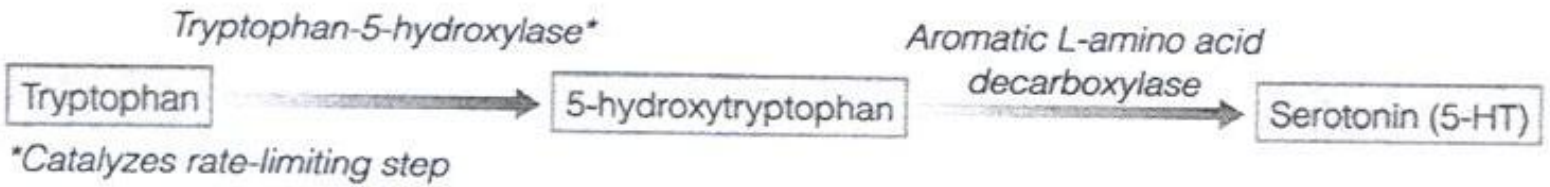
- Serotonin is formed by the hydroxylation and decarboxylation of **tryptophan**

- After release, it is recaptured by an active, reuptake mechanism and inactivated by *Monoamino Oxidase* **(MAO) enzyme .**

[As mentioned before , it is believed that decreased synaptic activity of Serotonin & Norepinephrine can cause **depression.**]



Serotonin



▪Serotonin

• **MAOI (Monoamine Oxidase Inhibitor drugs) :**

Block MAO enzyme → increase synaptic Serotonin & Norepinephrine

[MAOIs are some of the most effective Antidepressant Drugs]

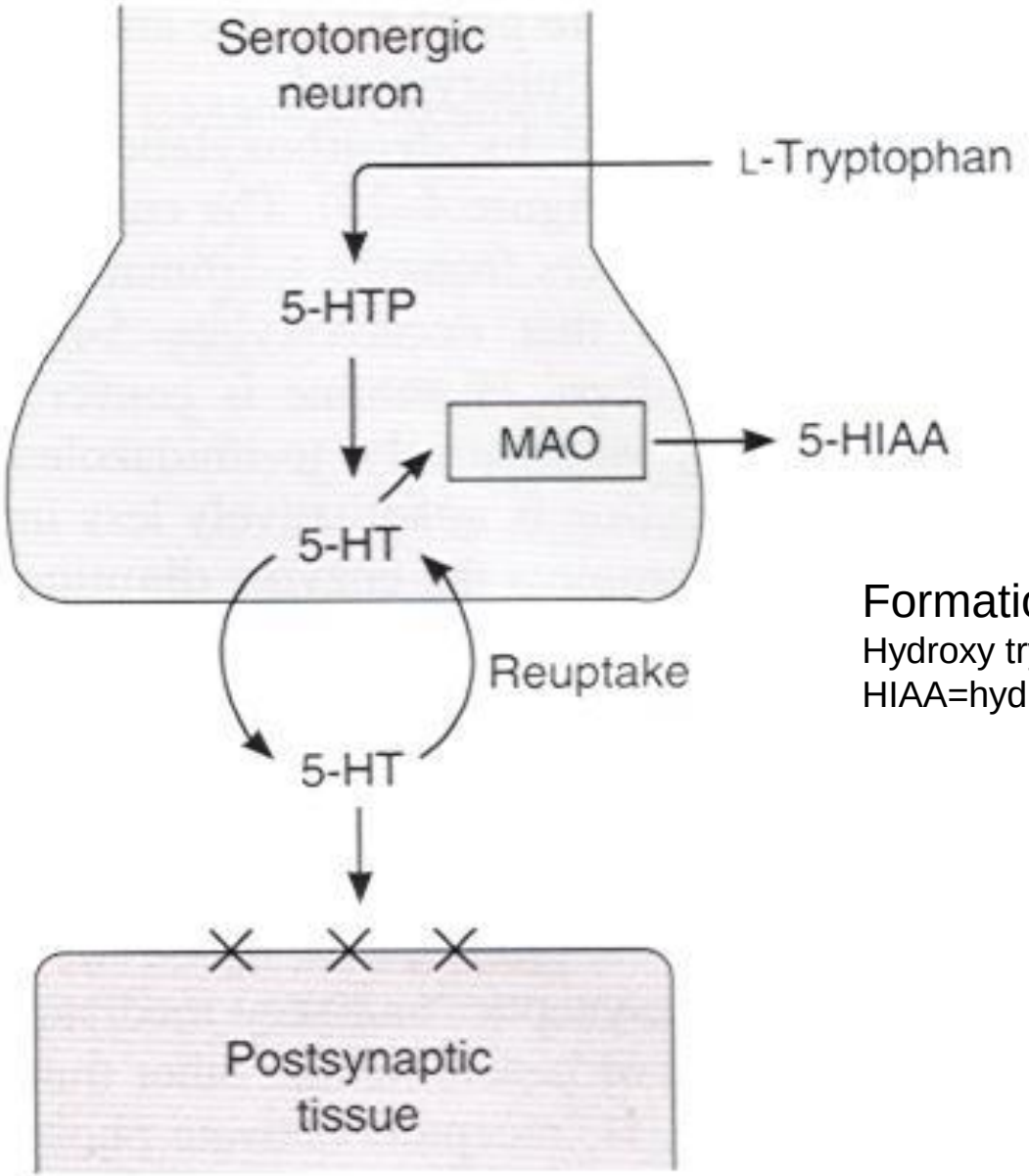
• Drugs that inhibit serotonin uptake such as Fluoxetine (Prozac) are also effective antidepressants.

• Whereas decreased serotonin activity causes depression ,[increased serotonin activity can induce hallucinations]

• The hallucinogenic drug Lysergic Acid Diethylamide **(LSD) is a serotonin agonist that** produces its effect by activating 5-HT2 receptors in the brain

•Serotonin Functions

- plays a very important role in a range of brain functions including :
  - Mood control
  - Regulation of sleep
  - Pain perception
  - Body temperature



Formation of serotonin =5-HT

Hydroxy tryptamine

HIAA=hydroxyindoleacetic acid

Neuro-transmitters	Precursor, enzymes	Receptors	Areas of concentration	Related disorders
Acetylcholine (Ach)	Choline, Choline-*O*-acetyltransferase	Nicotinic Muscarinic	Basal nucleus of Meynert, Limbic system, NM junctions, Parasympathetic neurons, Autonomic ganglia	Alzheimer disease, Myasthenia gravis, Botulism
Dopamine	Phenylalanine, Tyrosine hydroxylase DOPA decarboxylase	D1 D2 (main receptors) D3, D4, D5	Nigrostriatal pathway, Hypothalamus	Parkinson disease, Prolactinoma, Schizophrenia
Norepinephrine (NE)	Phenylalanine, Tyrosine hydroxylase Dopamine-β-hydroxylase	α-receptor β-receptor	Locus coeruleus, Lateral tegmental nuclei, Sympathetic ganglia	Sleep-wake cycle
Glutamate	α-Ketoglutarate, Glutamate dehydrogenase	NMDA, Kainate, AMPA	Cerebral cortex, Brainstem, Spinal cord, Hippocampus	Epilepsy, Migraine, Stroke
Gamma-aminobutyric acid (GABA)	Glutamate, Glutamic acid decarboxylase (GAD)	$GABA_A$ $GABA_B$	Striatonigral system, Cerebellum, Hippocampus, Cerebral cortex	Sleep, Epilepsy Anxiety
Glycine	Serine		Spinal cord, Brainstem	Tetanus, Strychnine poisoning
Serotonin	Tryptophan, Tryptophan hydroxylase		Raphe nuclei	Levels of arousal, Pain modulation, Migraine, Depression

▪Histamine

- Histamine forming cells are in posterior hypothalamus also found in gastric mucosa and in mast cells.
- Formed by decarboxylation of amino acid histidine with the help of enzyme histaminase.

- Three known types of histamine receptors in found e.g. H_1, H_2, H_3.

- H_3 receptors are presynaptic.

Its function in brain is not very certain. Its main function is that it is excitatory.

- **Excitatory Amino Acids (Glutamate and Aspartate)**

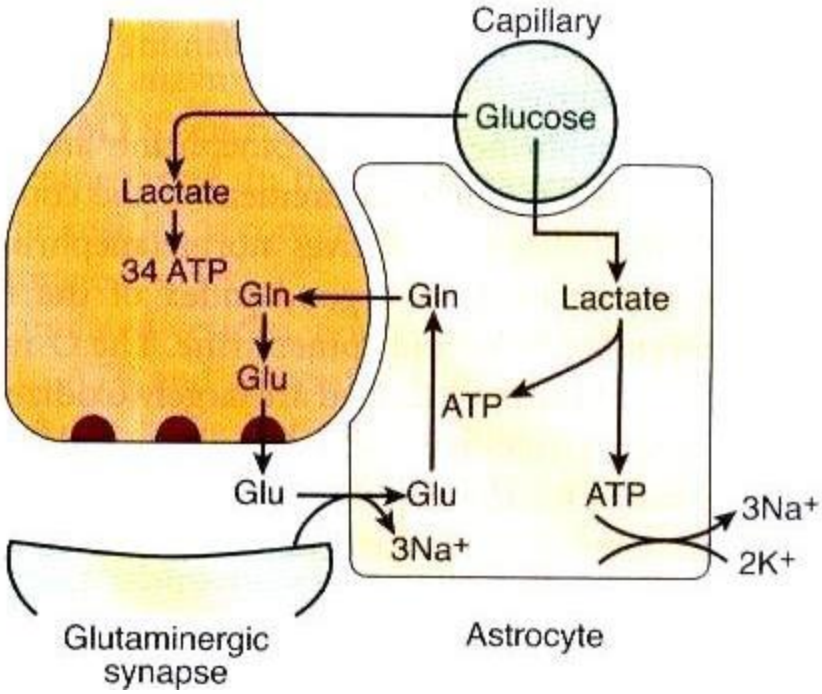
▪Glutamic acid / Glutamate

- It is the most commonly found neurotransmitter in the brain.
- It is always excitatory.
- Glutamate is neurotoxic while glutamine is not.
- There are two types of receptors e.g. metabotropic and iontropic receptors.

▪Glutamate

Glutamate is formed during Kreb's cycle by *reductive amination* of alpha-ketoglutarate in the cytoplasm

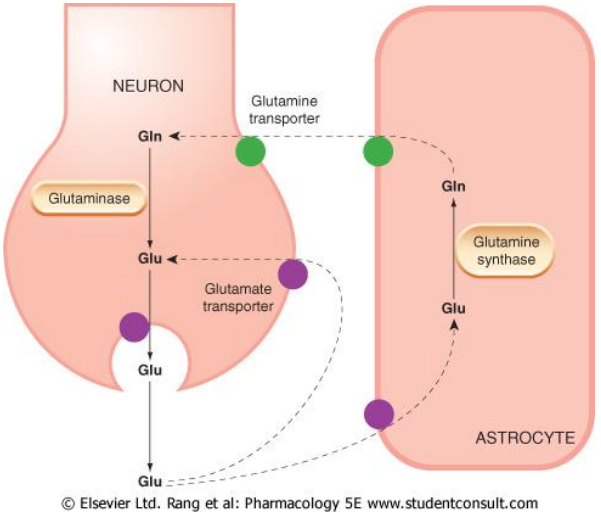
- Then , it is concentrated in synaptic vesicles by the vesicle-bound transporter BPN1 .
- When released , it is taken up by Astrocytes and converted to **glutamine**
- Then this glutamine passes back to the neurons and is converted back to Glutamate, which is again released as a synaptic transmitter.
- Thus the main mechanism of removal of Glutamate from synapses is uptake into ***Astrocytes and neurons***



- **Transport of glutamate (Glu) and glutamine (Gln) by *neurons and astrocytes.***

- **Released glutamate is captured partly by neurons and partly by astrocytes, which convert it to glutamine.**

- **Astrocytes release glutamine via a transporter, and neurons take it up and synthesise glutamate.**



•Roles In Health And Disease

In Health:

Glutamate NMDA receptor is involved in Long-Term Potentiation & memory storage .

In Disease :

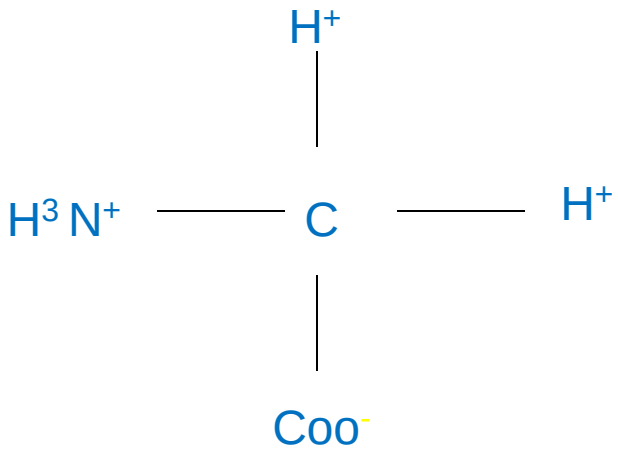
• (1) Excess Glutamate activity is implicated in some types of epileptic Seizures

• (2) Under some pathological conditions , such as Stroke , ALS (Amyotrophic Lateral Sclerosis) and Alzheimer's diseases, it acts as an exotoxin → producing excessive influx of calcium into the neurons → causing neuronal death .

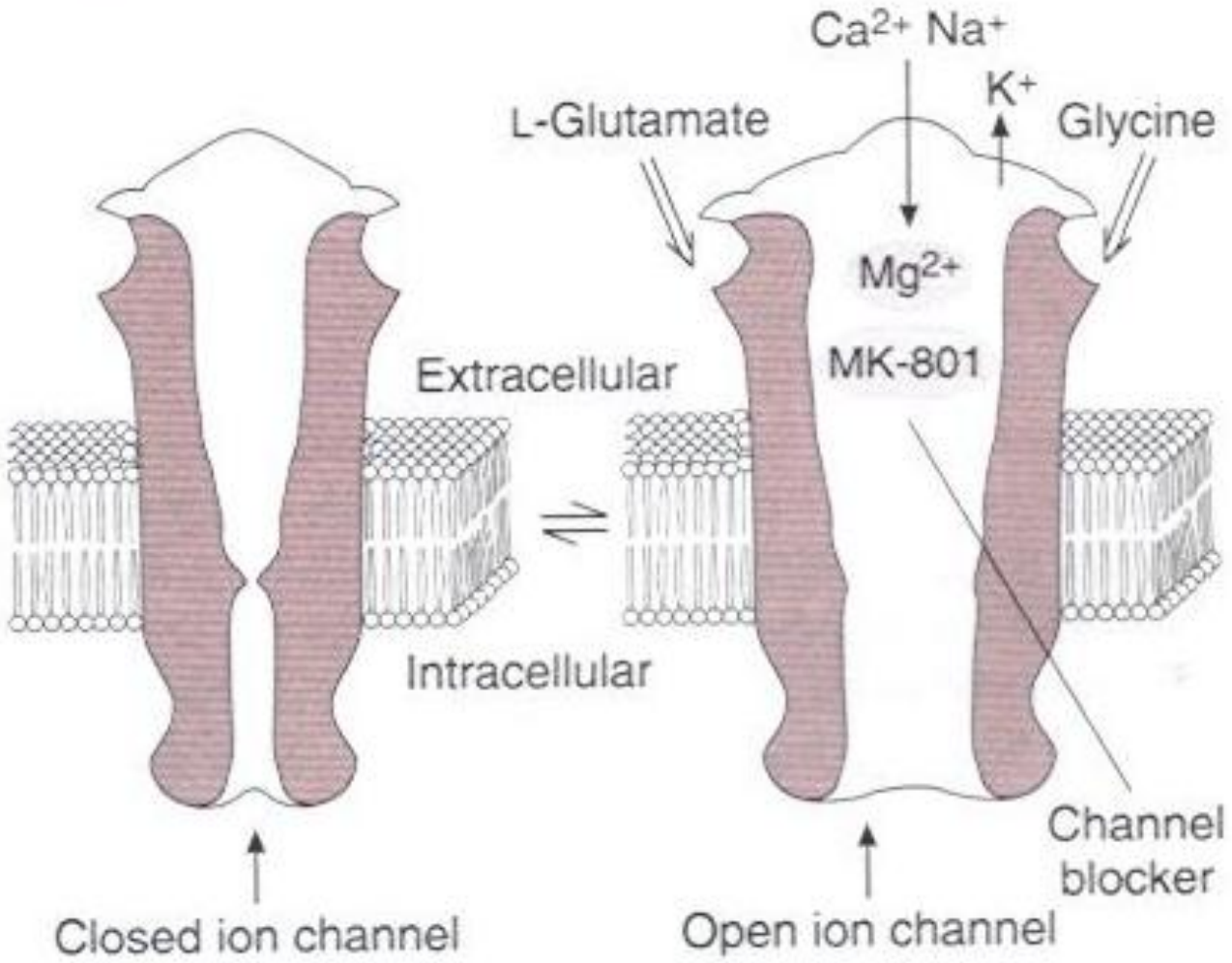
- **Inhibitory Amino Acids (GABA, Glycine)**

▪Glycine

- It is simplest of all aminoacids, consisting of amino group and a carboxyl group attached to a carbon atom



- Its an inhibitory neurotransmitter.
- It binds to a receptor which makes the postsynaptic membrane more permeable to Cl^- Ion and cause hyperpolarization (inhibition).
- The glycine receptor is primarily found in the ventral part of the spinal cord.
- Strychnine is glycine antagonist.



NMDA =N methyl-D-aspartate receptors, when glutamate & glycine bind to receptor ion channels open, Mg block channels

▪Gamma Aminobutyric acid (GABA)

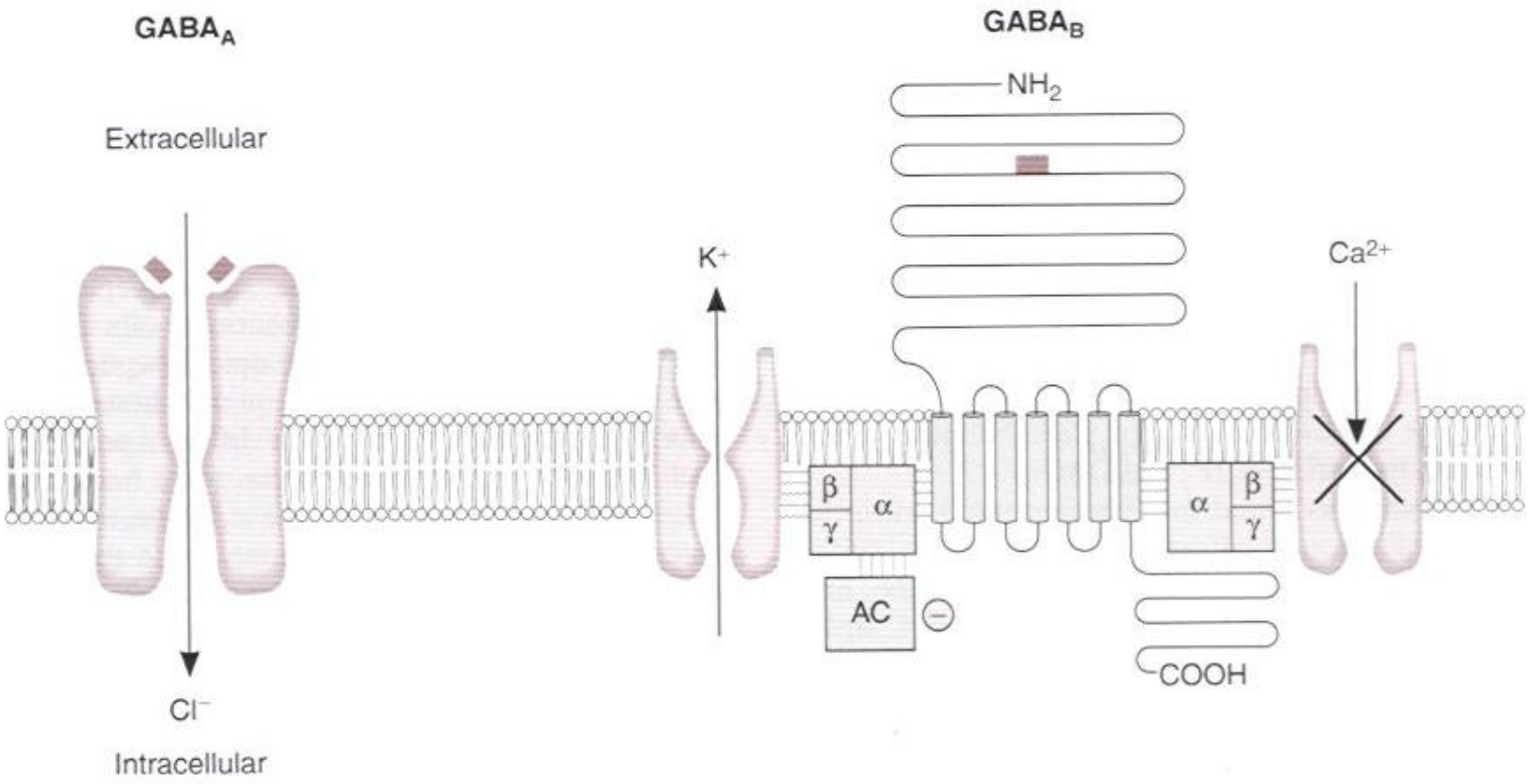
- Major inhibitory neurotransmitter of CNS and is also found in retina.
- Formed by decarboxylation of glutamate.

The enzyme that catalyzes this reaction is Glutamate Decarboxylase (GAD, Glutamic Acid Decarboxylase).

- GAD is present in the nerve ending.

- **Three types of GABA receptors :**

1. GABA $_{A \& B}$ receptors are widely distributed in CNS.
2. $GABA_C$ are found in retina only.
3. GABA $_B$ are metabotropic (G-protein) in function.


GABA$_A$
GABA$_B$
Extracellular
NH_2
K^+
Ca^{2+}
β
α
γ
α
β
γ
AC
⊖
COOH
Cl^-
Intracellular

▪GABA cont.

- Inactivation : by 2 ways:

(1) GABA is metabolized by the enzyme GABA Transaminase (GABA-T).

(2) In addition, there is active reuptake of GABA

- ***GABA acts by***

(1) increasing Chloride influx

(2) increasing Potassium efflux

(3) decreasing Calcium influx

[all these hyperpolarize the neuron and produce IPSP]

•Functions and Medical Uses of GABA

The increase in chloride conductance produced by GABAa receptors is potentiated by members of the **Benzodiazepinethe family** of drugs such as Diazepam (Valium) .

- **Medical uses of Benzodiazepines include :**

(1) Anxiolytic (anti-anxiety) /sedatives

(2) Muscle relaxants , and

(3) Anticonvulsants

▪OPIOD PEPTIDES

- Brain and GIT contain receptors that bind Morphine.
- Endogenous ligands for these receptors (opoiod) are called ***enkaphalins***.

- Peptides that bind to opiod receptors are called **opiod peptides.**

- Opiod receptors are: μ, Ќ, б. They all inhibit adenyl cyclase.

- **Opoiod Peptides**

-μ:

Site of action of morphine,analgesia, respiratory depression, constipation, euphoria, sedation, miosis

- Ќ:

Analgesia, sedation

-б : Analgesia

▪Enkephalins/Endorphins

- **Found in :**

1-*GIT nerve endings, brain, substantia* gelatinosa.

2- Anterior and intermediate lobes of pituitary gland secrete the precursor: Pro-opiomelanocortin, which contains b-endorphin.

- Endorphins are also produced by :

3- neurons in hypothalamus, limbic system, brain- stem.

They are involved in various functions including: tolerance, and addiction produced by morphine.

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
1.Acetyl choline (Ach)	Excitatory	Acetyl co-A + Choline	Cholinergic nerve endings Cholinergic pathways of brainstem	1.Nicotinic 2.Muscarinic	Broken by acetyl cholinesterase	Cognitive functions e.g. memory Peripheral action e.g. cardiovascular system
2. Catecholamines i. Epinephrine (adrenaline)	Excitatory in some but inhibitory in other	Tyrosine produced in liver from phenylalanine	Adrenal medulla and some CNS cells	Excites both alpha α & beta β receptors	1.Catabolized to inactive product through COMT & MAO in liver 2.Reuptake into adrenergic nerve endings 3.Diffusion away from nerve endings to body fluid	For details refer ANS. e.g. fight or flight, on heart, BP, gastrointestinal activity etc. Norepinehrine controls attention & arousal.
ii.Norepinephrine	Excitatory	Tyrosine, found in pons. Reticular formation, locus coerules, thalamus, mid-brain	Begins inside axoplasm of adrenergic nerve ending is completed inside the secretary vesicles	α_1 α_2 β_1 β_2		
iii. Dopamine	Excitatory	Tyrosine	CNS, concentrated in basal ganglia and dopamine pathways e.g. nigrostriatal, mesocorticolimbic and tubero-hypophyseal pathway	D_1 to D_5 receptor	Same as above	Decreased dopamine in parkinson's disease. Increased dopamine concentration causes schizophrenia

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
3. serotonin (5HT)	Excitatory	Tryptophan	CNS, Gut (chromaffin cells) Platelets & retina	5-HT_1 to 5-HT_7 5-HT_2A receptor mediate platelet aggregation & smooth muscle contraction	Inactivated by MAO to form 5-hydroxyindoleacetic acid(5-HIAA) in pineal body it is converted to melatonin	Mood control, sleep, pain feeling, temperature, BP, & hormonal activity
4. Histamine	Excitatory	Histidine	Hypothalamus	Three types H_1, H_2, H_3 receptors found in peripheral tissues & the brain	Enzyme diamine oxidase (histaminase) cause breakdown	Arousal, pain threshold, blood pressure, blood flow control, gut secretion, allergic reaction (involved in sensation of itch)
5. Glutamate	Excitatory 75% of excitatory transmission in the brain	By reductive amination of Kreb's cycle intermediate α –ketoglutarate.	Brain & spinal cord e.g. hippocampus	Ionotropic and metabotropic receptors. Three types of ionotropic receptors e.g. NMDA, AMPA and kainate receptors.	It is cleared from the brain ECF by Na^+ dependent uptake system in neurons and neuroglia.	Long term potentiation involved in memory and learning by causing Ca^{++} influx.

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
6. Aspartate	Excitatory	Acidic amines	Spinal cord	Spinal cord	Aspartate & Glycine form an excitatory / inhibitory pair in the ventral spinal cord	
7. Gama amino butyric acid(GABA)	Major inhibitory mediator	Decarboxylation of glutamate by glutamate decarboxylase (GAD) by GABAergic neuron.	CNS	GABA – A increases the Cl^- conductance, GABA – B is metabotropic works with G – protein GABA transaminase catalyzes. GABA – C found exclusively in the retina.	Metabolized by transamination to succinate in the citric acid cycle.	GABA – A causes hyperpolarization (inhibition) Anxiolytic drugs like benzodiazepine cause increase in Cl^- entry into the cell & cause soothing effects. GABA – B cause increase conductance of K^+ into the cell.
8. Glycine	Inhibitory	Is simple amino acid having amino group and a carboxyl group attached to a carbon atom	Spinal cord	Glycine receptor makes postsynaptic membrane more permeable to Cl^- ion.	Deactivated in the synapse by simple process of reabsorbtion by active transport back into the presynaptic membrane	Glycine is inhibitory transmitted found in the ventral spinal cord. It is inhibitory transmitter to Renshaw cells.

TABLE 2-1 Excitatory Neurotransmitters

Excitatory Neurotransmitters	Properties
Acetylcholine	• Used for signaling by "***cholinergic***" neurons (in the autonomic nervous system, ***all preganglionic neurons***, as well as parasympathetic ***postganglionic neurons***, signal with acetylcholine) • Used at ***neuromuscular junction*** • Bind muscarinic and nicotinic receptors • Degraded by ***acetylcholinesterase***
Dopamine	• Binds D1 and D2 receptors • Synthesized from tyrosine • Four major tracts use dopamine, three of which are in the substantia nigra and are involved in ***Parkinson's disease*** and other movement disorders
Norepinephrine/Epinephrine	• Used by "***adrenergic***" neurons in sympathetic nervous system (see Chapter 8, Autonomic Nervous System) • Synthesized from dopamine
Serotonin	• Binds 5-HT receptors • Implicated in depressive and anxiety disorders
Glutamate	• Most common neurotransmitter in the brain • Binds N-methyl-D-aspartate (NMDA) receptors • Always excitatory; glutamate excitotoxicity has been implicated as important cause of ischemic, anoxic, epileptic, and traumatic neuronal damage

Applications:

1. Presynaptic effect

i) Botulinum toxin:

It's an exotoxin that binds to the presynaptic membrane

- prevents the release of Ach resulting in weakness and reduction of tone.

- It is used to control dystonia in which body shows overactive muscular activity.
- cosmotic purposes.

ii) Lumbert – Eaton syndrome

Antibodies directed against Ca^{++} channels located in presynaptic terminals and interfere with transmitter release causing weakness.

iii)Neuromyotonia:

Patient complains of muscle spasm and stiffness resulting in continuous motor activity in the muscle.

It is caused by antibody directed against the presynaptic voltage gated K^{+} channel so that the nerve terminal is always in a state of depolarization.

2. Effects at Postsynaptic level:

i) Curare

binds to the acetylcholine receptor (AchR) and prevents Ach from acting on its receptor and so that it induces paralysis.

i) Myasthenia gravis:

is caused by an antibody against the Ach receptors and Ach receptors are reduced hence the Ach released has few Ach receptor available to work and patients complain of weakness that increases with exercise.

Aneasthesia

- Alcohols, barbiturates and many volatile anesthetics act on ion channel receptors and specifically on GABAa, and glycine receptors to increase CL- conductance.

- Other anesthetics act by inhibiting NMDA and AMPA receptors.

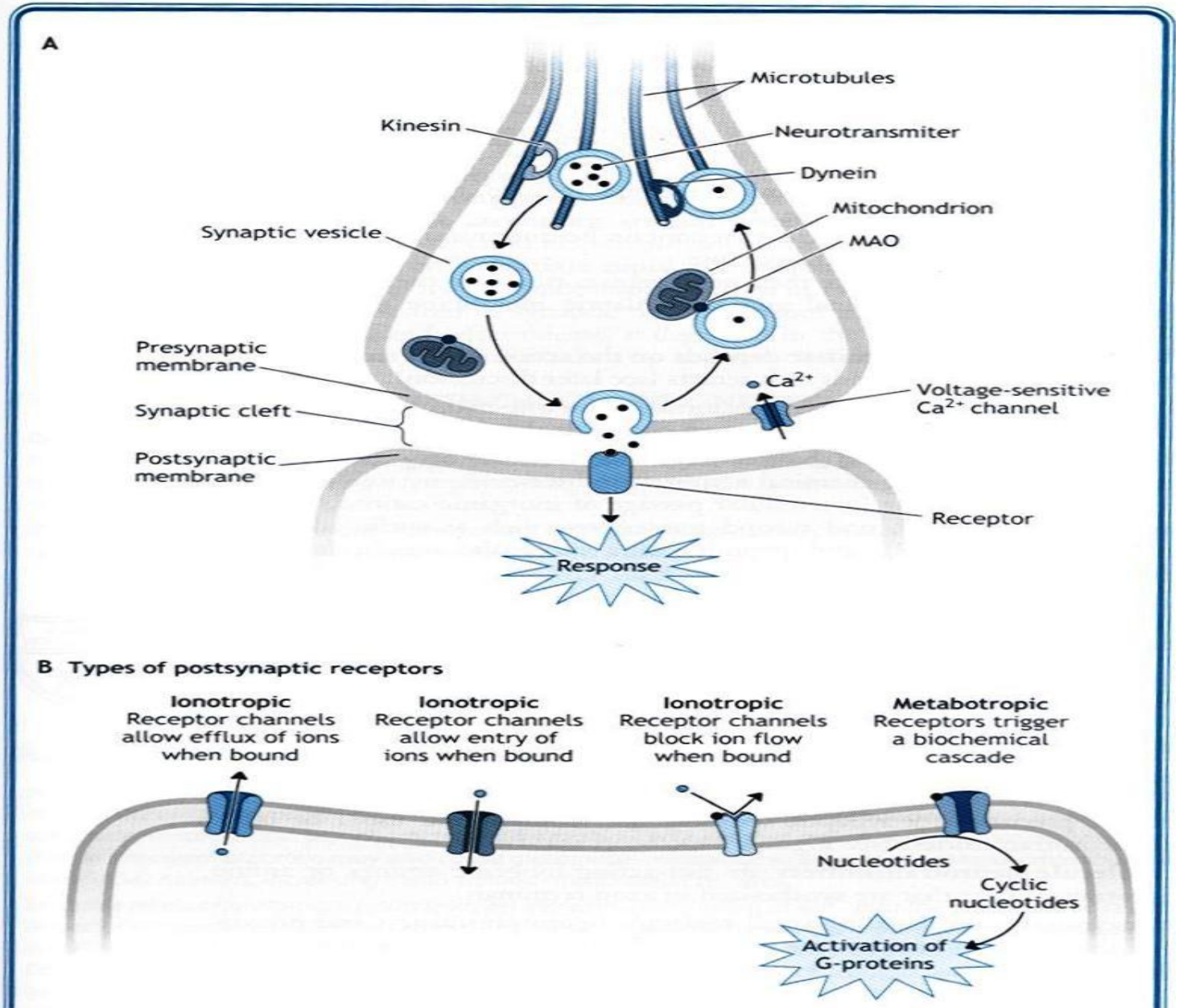
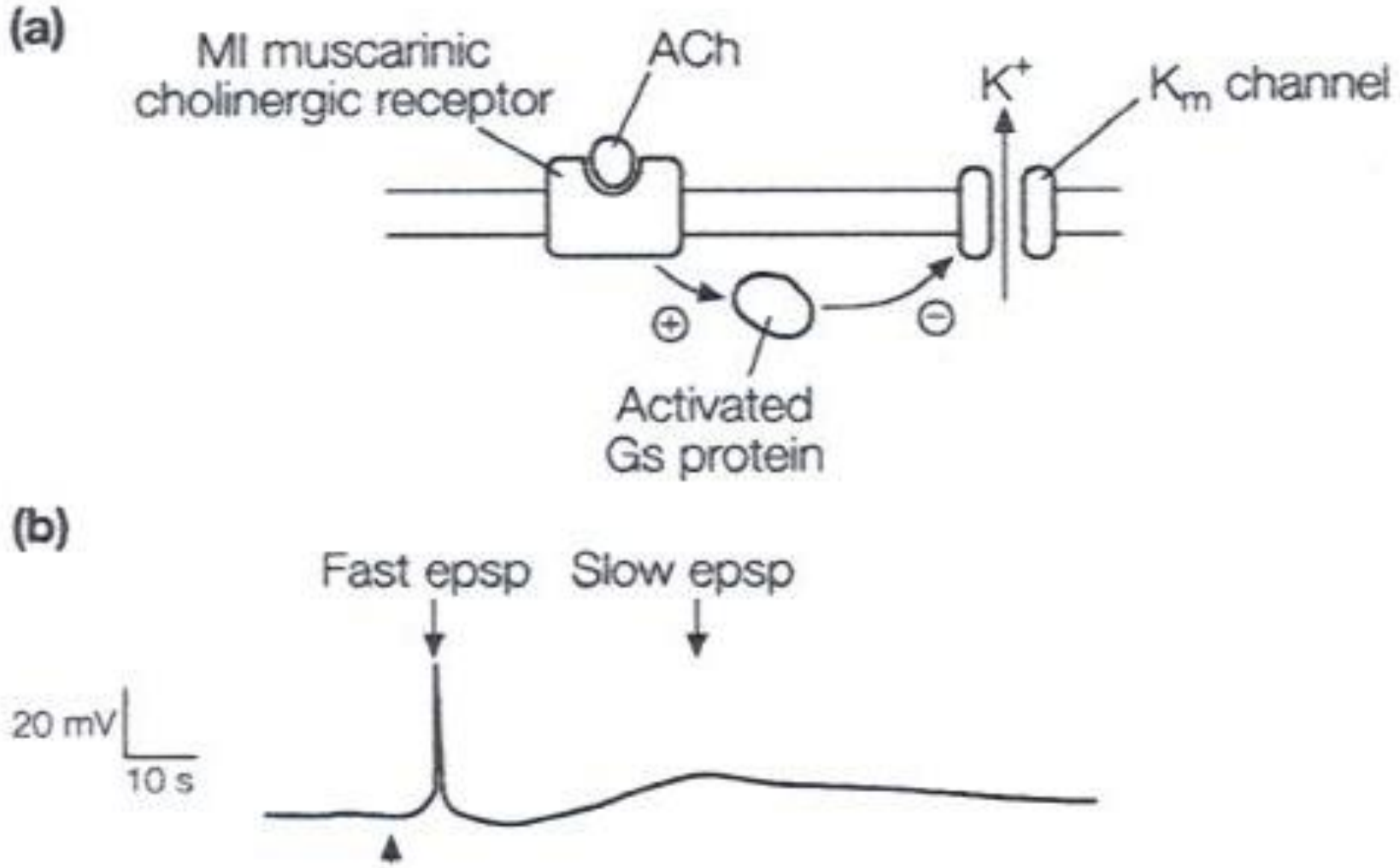


Figure 2–6. **A** and **B:** Types of postsynaptic receptors and features of a synapse.


(a)
MI muscarinic
cholinergic receptor
ACh
K+
Km channel
⊕
⊖
Activated
Gs protein
(b)
Fast epsp
Slow epsp
20 mV
10 s